



Ending TB in North Dakota

Finding and Treating TB

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Barbara Seaworth has the following disclosures to make:

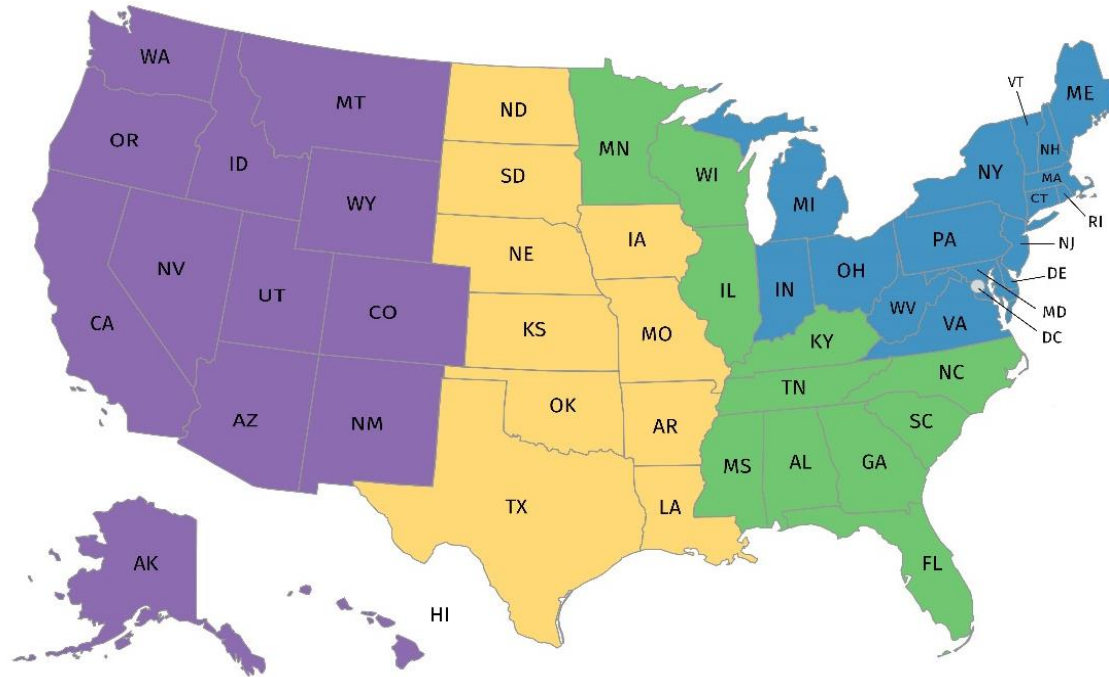
- No conflict of interests
- No relevant financial relationships with any commercial companies



CDC Funded Centers of Excellence

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- Kansas
- Louisiana
- Missouri
- Nebraska
- North Dakota
- Oklahoma
- South Dakota
- Texas
- City of Houston

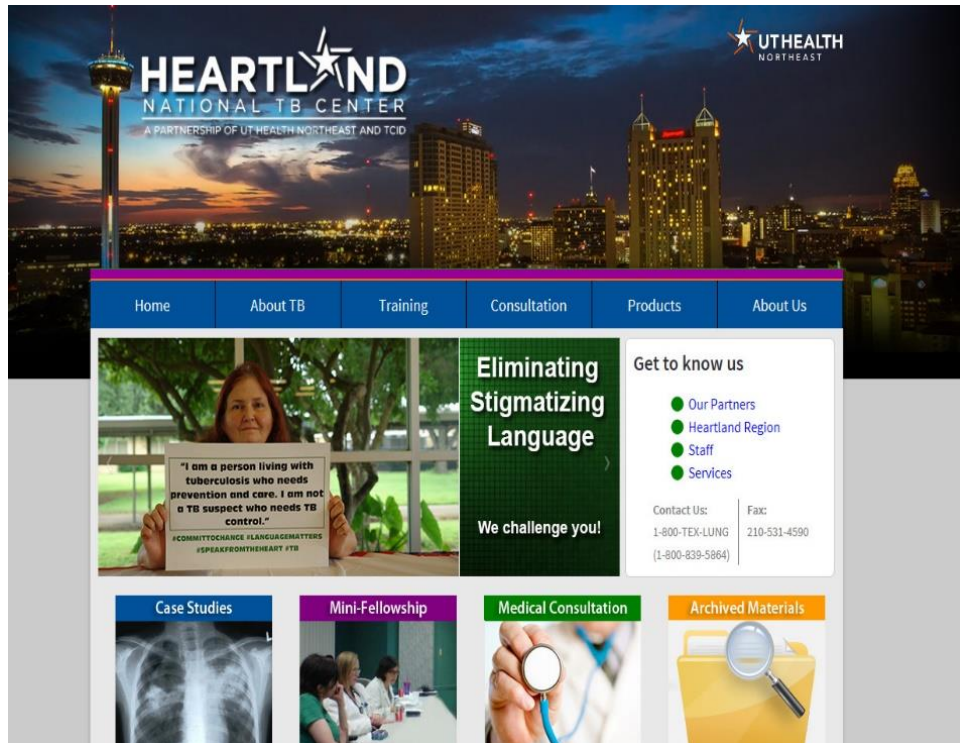


- [Curry International Tuberculosis Center](#)
- [Heartland National Tuberculosis Center](#)
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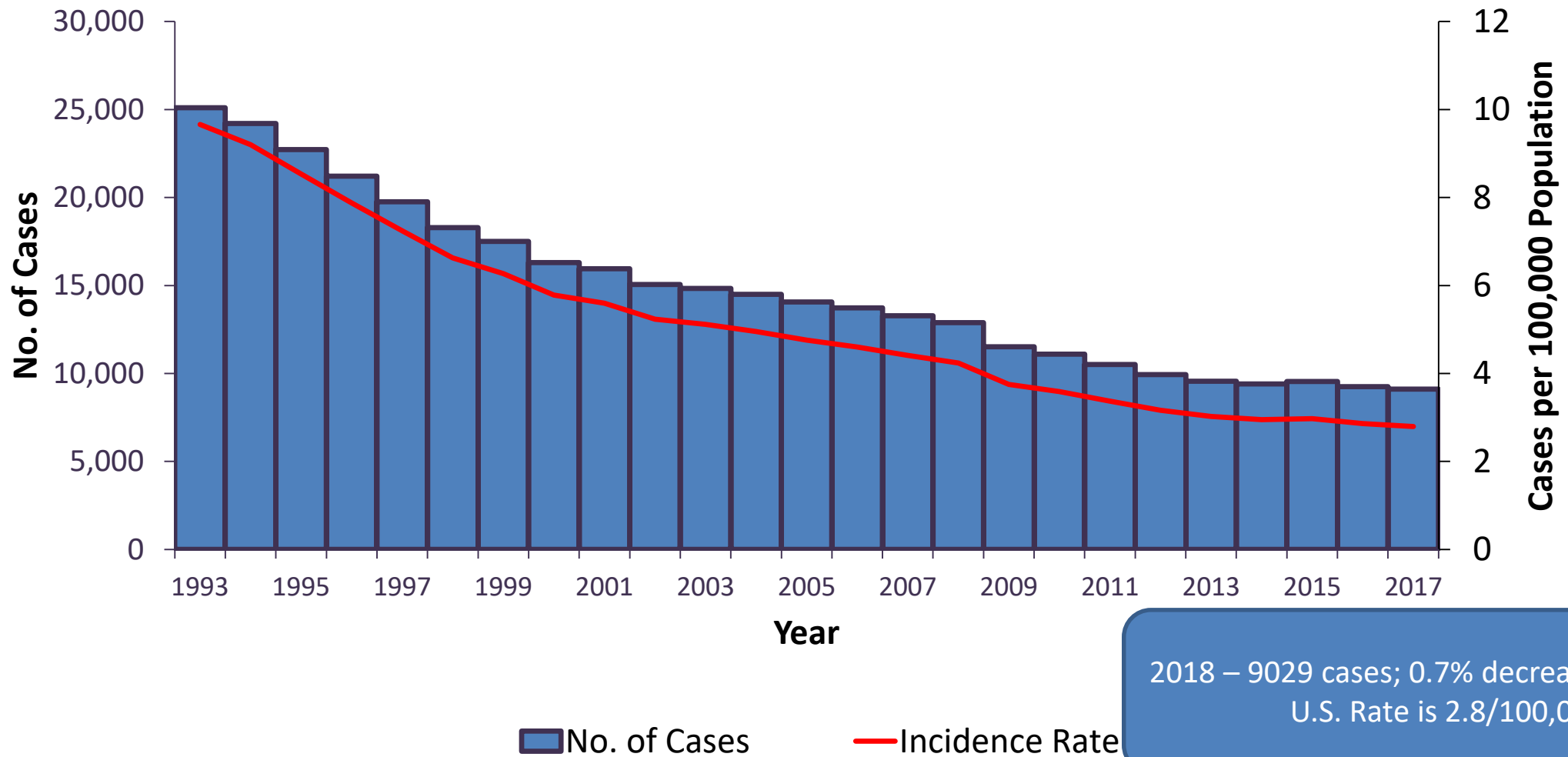
WHO – What – Why

Involved with Diagnosing Tuberculosis

- WHO
 - Is at risk of TB exposure?
 - Is at risk of TB infection?
 - Is at risk of progression to TB disease?
- What are the diagnostic tools?
- Why
 - Do we target specific groups for screening
 - Do we target specific groups for treatment
- Why do I want to learn how to diagnose TB?



Reported Tuberculosis (TB) Cases and Rates United States, 1993–2017



TB Case Rates,* United States, 2017

*Cases per 100,000
DC, District of Columbia; NYC, New York City (excluded from New York state)

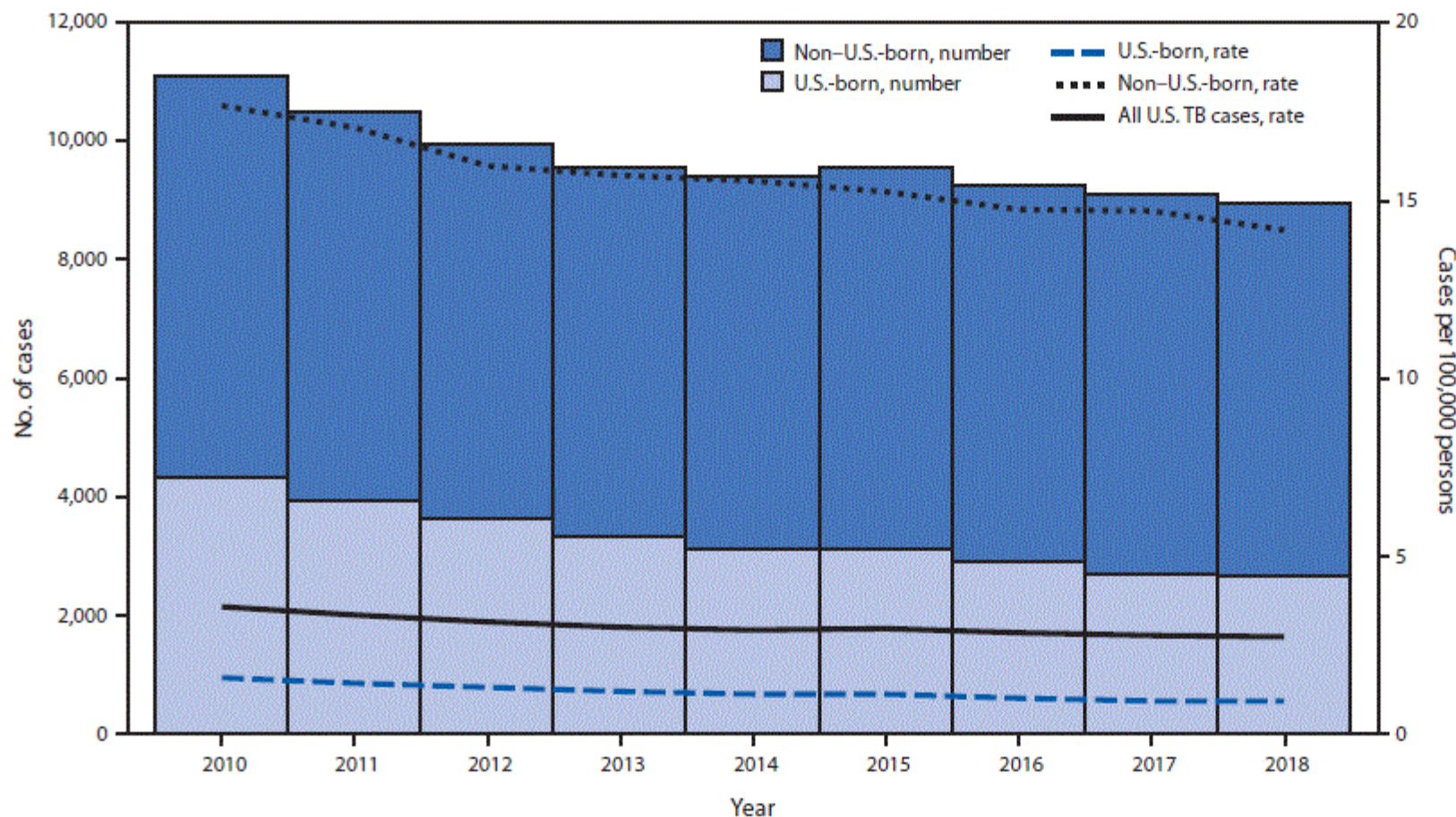
Legend:
Yellow: ≤ 2.8 (2017 national average)
Blue: > 2.8

NYC
DC

In 2017, TB Cases were reported in all 50 states and the District of Columbia.

DC, District of Columbia; NYC, New York City (excluded from New York state)

FIGURE. Number of tuberculosis (TB) cases and TB incidence, by national origin^{*,†} — United States, 2010–2018



* Number of cases among non-U.S.-born and U.S.-born persons and associated incidence exclude cases with unknown country of origin. Incidence for all U.S. TB cases includes cases with unknown country of origin.



Think TB

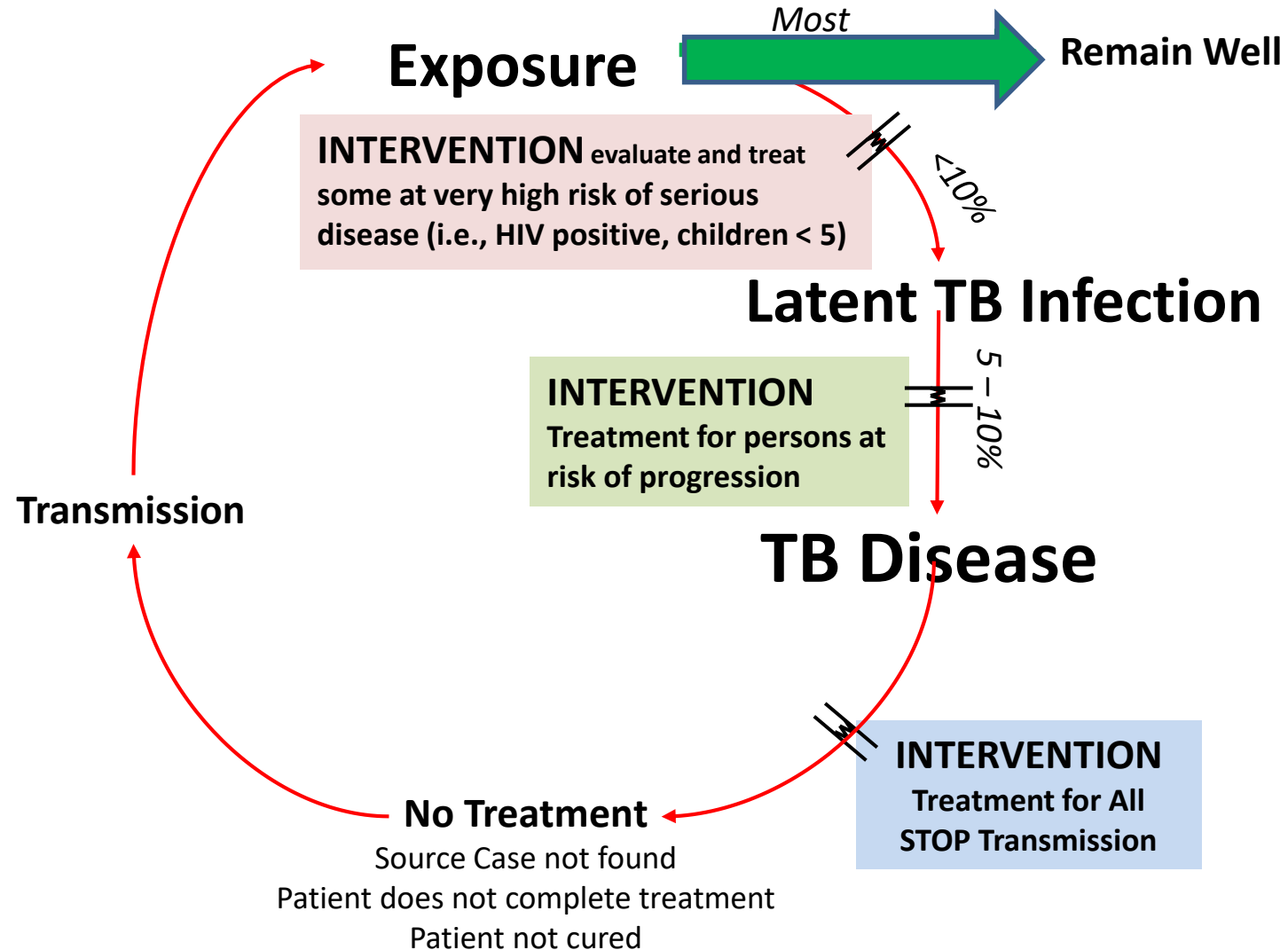
TREATMENT IS PREVENTION – WE DO NOT HAVE AN
EFFECTIVE VACCINE – YET

TREATMENT STOPS TRANSMISSION

YOU HAVE TO FIND THEM TO TREAT THEM!



Treatment is Prevention



Latent TB Infection (LTBI)

- Persons are infected with *Mycobacterium tuberculosis* but:
 - No Active TB Symptoms
 - Chest X-ray may be normal, or show granuloma, **stable** pleural or parenchymal scarring
 - Positive Tuberculin Skin Test (TST) or Blood Test

Active TB Disease

- Persons usually have at least one of the below
 - Abnormal CXR
 - Symptoms and or findings c/w TB disease
 - Positive specimen which is pcr positive or grows MTB
- Usually are infectious



LATENT TB INFECTION

- Persons with LTBI are NOT infectious
- 90 +% chance of never getting Active TB Disease
- But the TB organism is in your body!
- “...a state of **persistent immune response** to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB”

WHO Guidelines on the management of Latent Tuberculosis Infection 2015



LATENT TB INFECTION

- We used to think the bacteria were in a complete resting state or dormant but
 - TB Bacteria **are metabolically active and dividing**, but infection is controlled by the immune system.
- **Current methods of LTBI diagnosis are less than perfect**
- Active TB Disease may develop if immunity wanes.



The Spectrum of Activity of MTB –One Could Think of Popcorn



Who Should be Tested for TB?

TB is relatively rare – We can't test everyone

The simplified version:

- Persons who are at increased risk for *M. tuberculosis* infection
- Persons at increased risk for progression to active disease if infected with *M. tuberculosis* (even if not at increased exposure risk)
- Persons with symptoms of active TB disease (fever, night sweats, cough, and weight loss)
 - Some persons are tested for administrative reasons (e.g., mandatory employment testing)

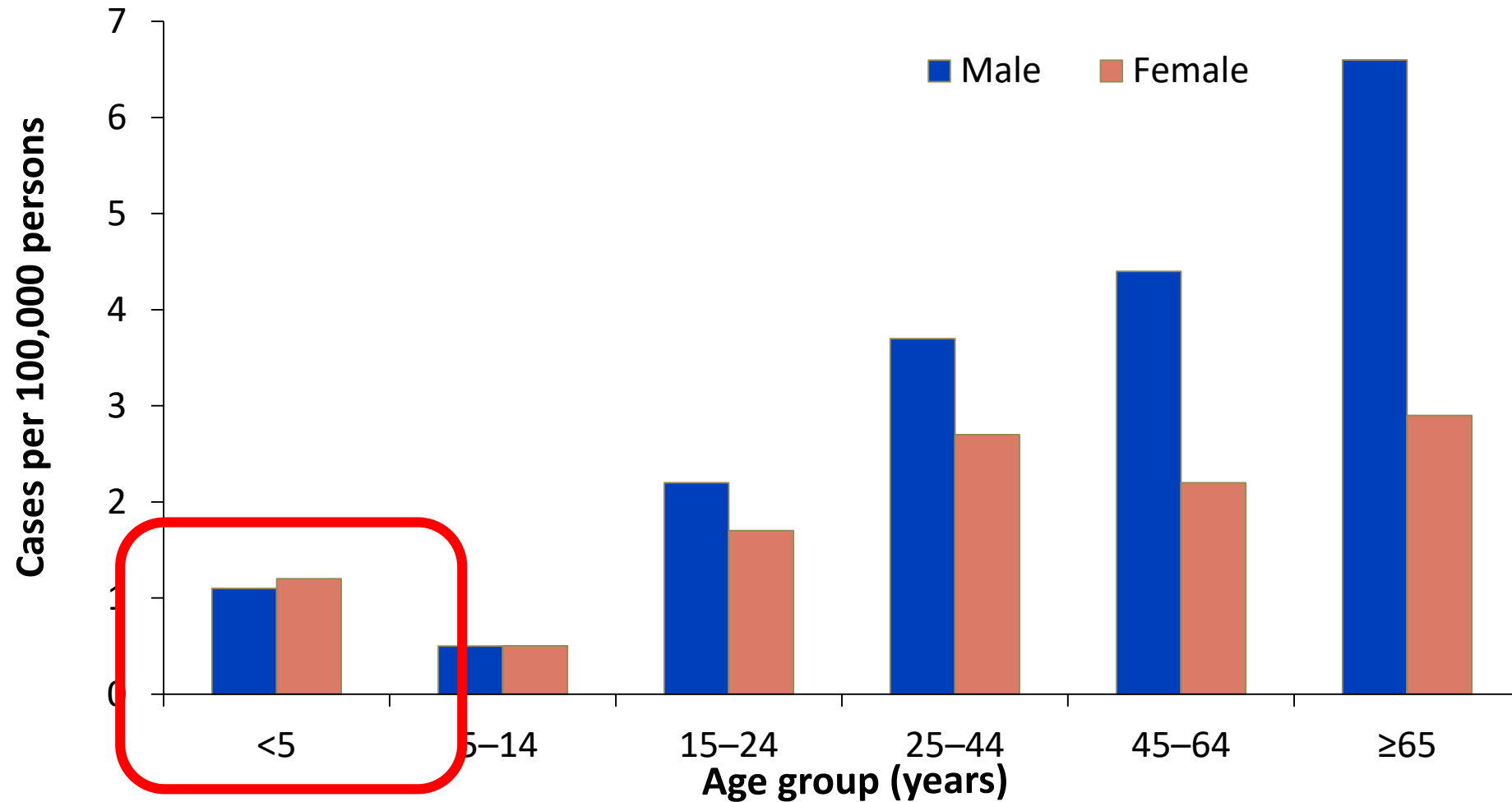


Persons at Risk of MTB Infection or Disease

- People who have spent time with someone who has TB disease
- People from a country where TB disease is common:
 - most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia
- People who live or work in high-risk settings:
 - correctional facilities, long-term care facilities or nursing homes, and homeless shelters
- Health-care workers who care for patients at increased risk for TB disease
- Infants, children and adolescents exposed to adults who are at increased risk for latent tuberculosis infection or TB disease



TB Case Rates by Age Group and Sex, United States, 2017*



*Cases per 100,000 population



TB Cases and Rates Among U.S.-Born versus Non-U.S.-Born Persons, United States, 1993–2017

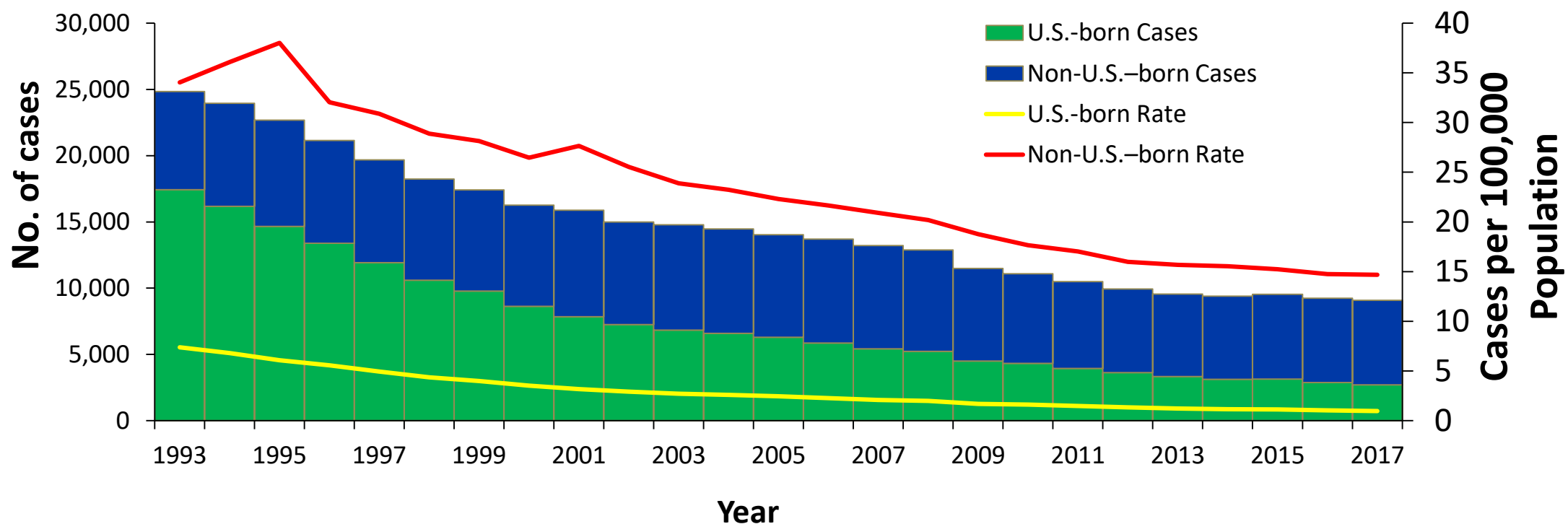
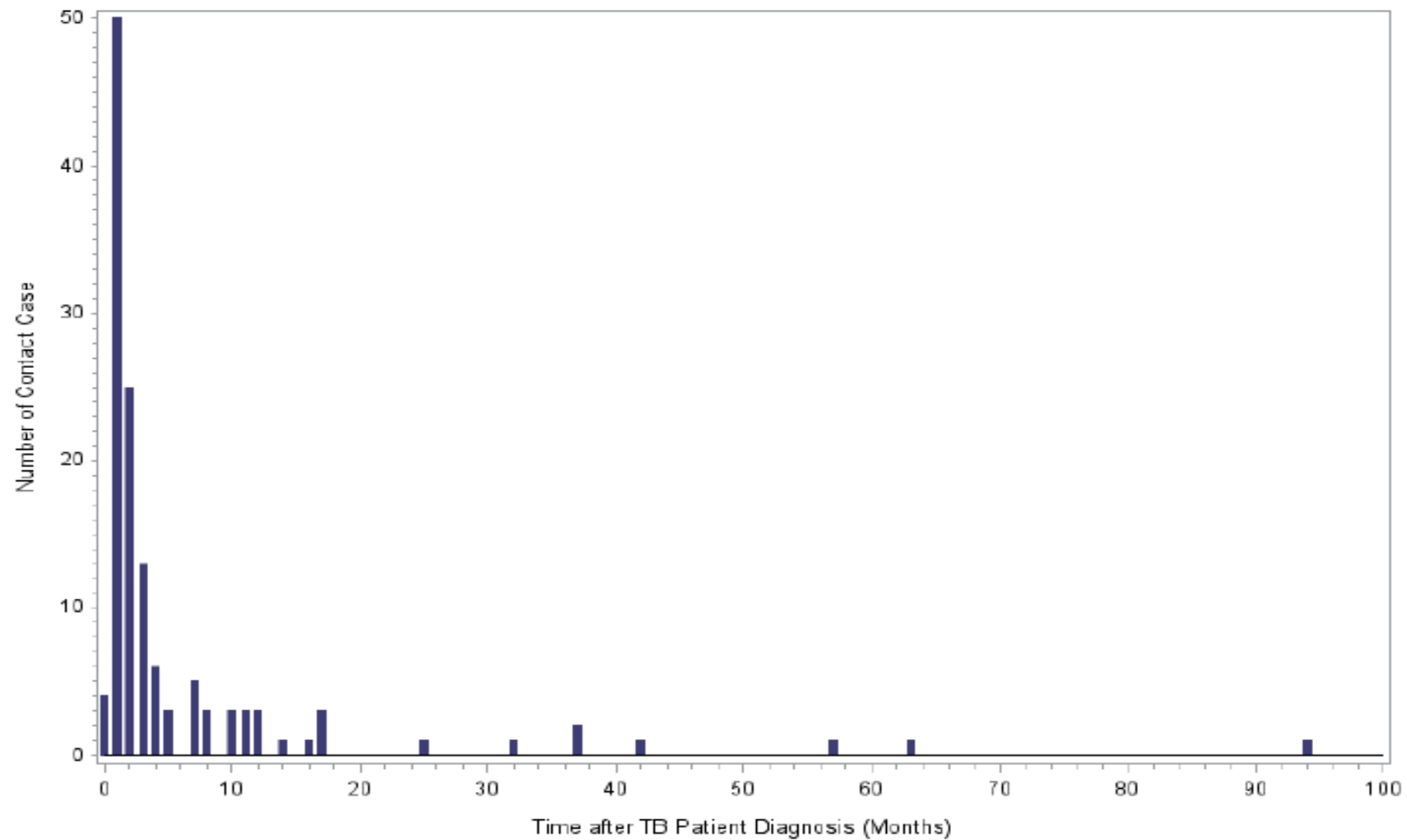


Figure 1. Timing of Tuberculosis Diagnosis among 131 Contacts Diagnosed after the Index Case Diagnosis



JID
June 2018



Persons at Risk of Progression from Latent TB Infection to Active TB Disease

- HIV infection
- Chronic kidney disease
- Silicosis
- **Recent exposure**
- Diabetes
- Chest x-ray abnormality c/w previous inadequately treated TB
- Intravenous drug use
- Smoking – active and passive
- Underweight by >10% (*Maybe*)

ATS-CDC. Am J Respir Crit Care Med 2000;161:S221



Persons at Risk of Progression from Latent TB Infection to Active TB Disease

- Immunosuppression
 - Pregnancy and first three months post partum
 - Organ transplant recipients
 - Hematologic cancers and head and neck cancers
 - Medications
 - TNF α inhibitors
 - Prednisone >15 mg, > 4 weeks
 - Chemotherapy
 - Other immunosuppressive drugs





Risk Factors For TB Disease

Of persons diagnosed with TB in 2017:

- 19.9% reported having diabetes 7.1%
- 8.9% reported excessive alcohol use 14.3%
- 5.5% were co-infected with HIV (of TB cases with HIV test results reported) 0%
- 6.7% reported using non-injectable drugs (1.2% reported using injecting drugs) 21.4%
- 4.6% reported being homeless in the past year 0%
- 3.1% were residents of correctional settings at time of diagnosis 0%

Contacts to an active case of TB 21.4%
Foreign born 50%

North Dakota rates



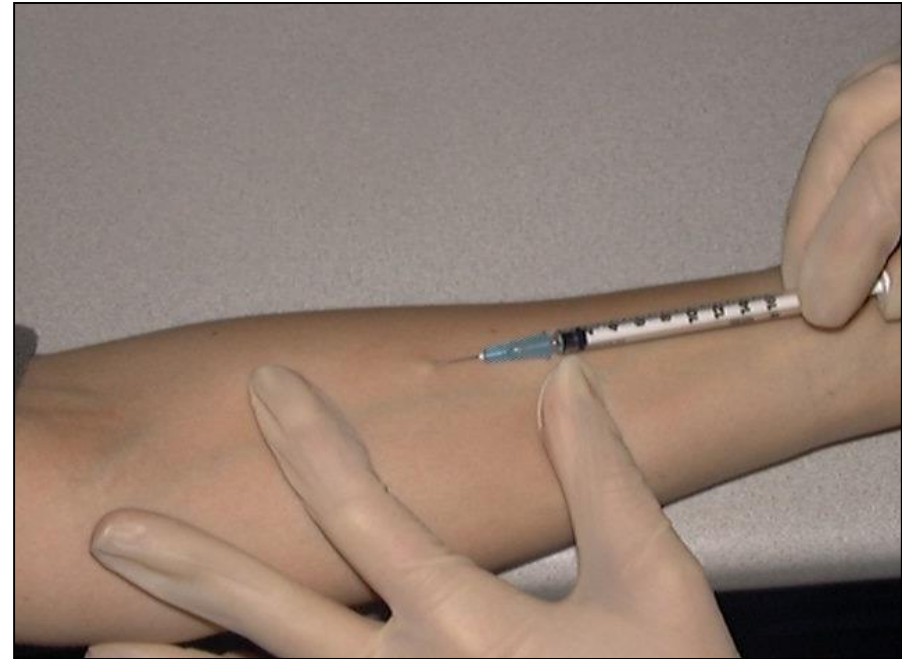
TB Infection Diagnostics

- In U.S. usually start with a screening test to detect evidence of TB infection – **After you Think of the Diagnostic Possibility**
 - TB Skin Test (**TST**)
 - Interferon Gamma Release Assays (IGRA)
 - Blood test



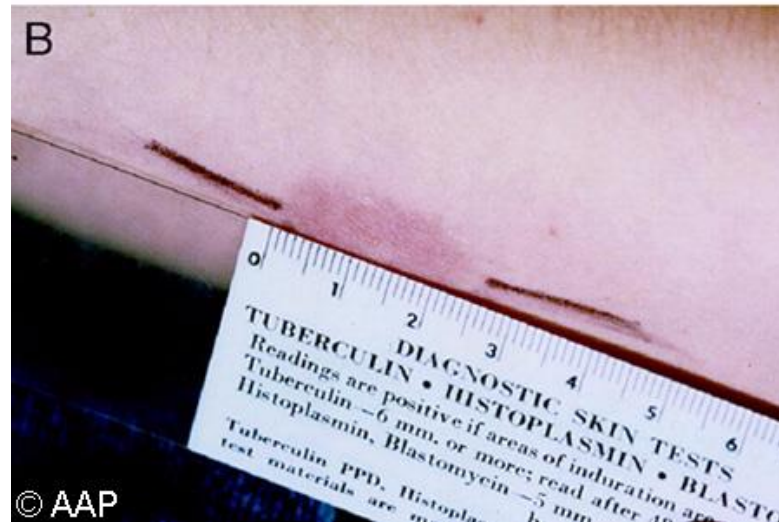
The Tuberculin Skin Test (TST)

- 0.1 ml of 5 TU PPD tuberculin injected intradermally
- **Induration** in millimeters read 48-72 hours after injection



Reading the TB Skin Test

Measure induration,
not erythema!!!



© AAP



TB Skin Test (TST)

- Pros:
 - Inexpensive
 - Simple to perform
(if you know what you are doing)
- Cons:
 - Must return in 48-72 hours
 - Interpretation is somewhat subjective
 - False Negatives:
 - Elderly
 - Immunosuppressed
 - False Positives:
 - Low risk populations
 - Non-tuberculous mycobacteria
 - BCG vaccination



Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients



Classifying the Tuberculin Reaction

10 mm is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories



Classifying the Tuberculin Reaction

15 mm is classified as positive in

- Persons with no known risk factors for TB
- Targeted skin testing programs should only be conducted among high-risk groups



INTERFERON GAMMA RELEASE ASSAYS (IGRAS)

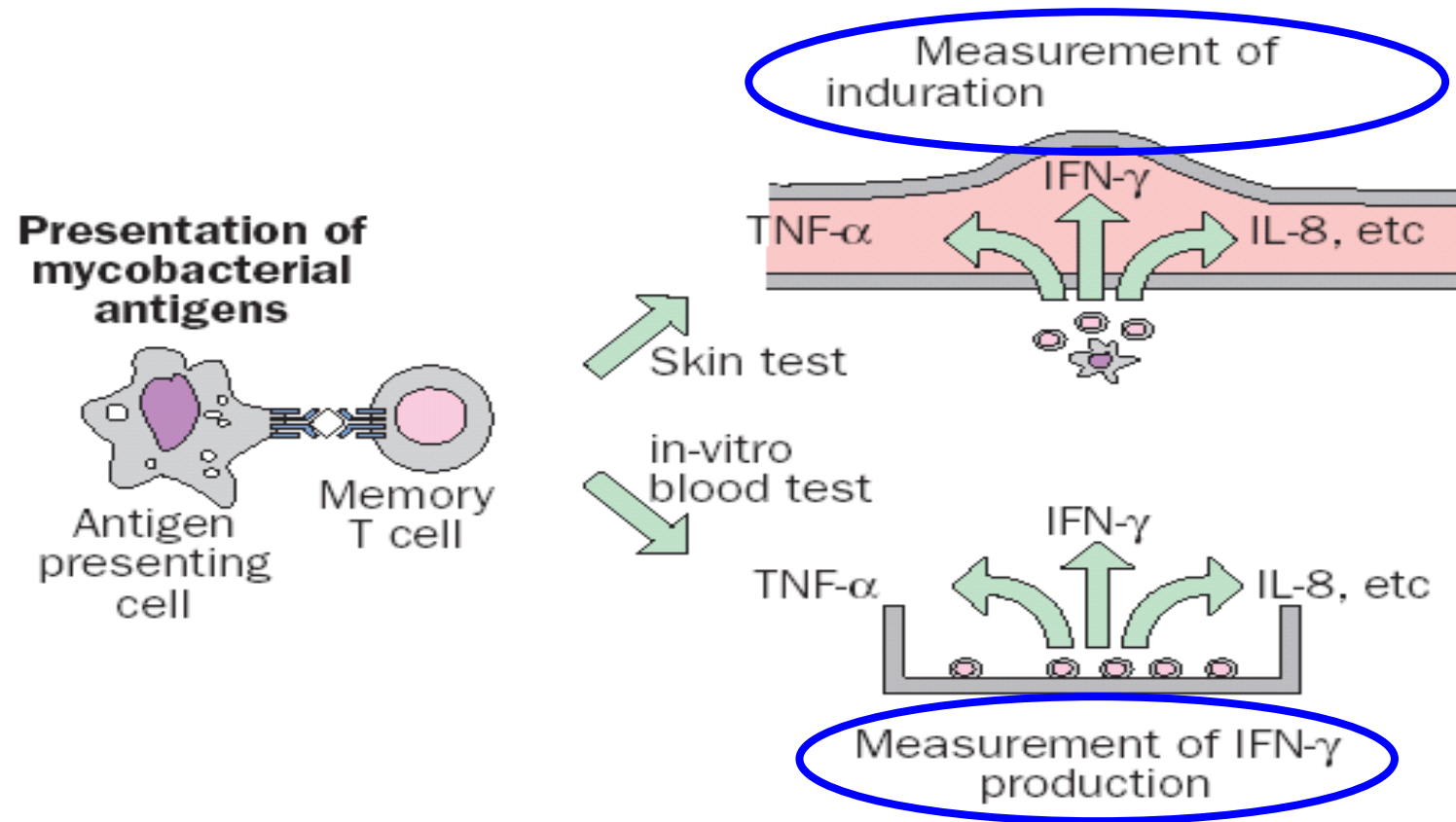


Diagnosis of LTBI

- Interferon Gamma Release Assays
 - Replacing TST in many jurisdictions
 - More specific
 - Equally sensitive
 - Do not require a patient to return for reading
 - Eliminate false positive TST due to BCG
 - Can be used in children down to 2 years of age



TST vs In-vitro Assays



Andersen et al. Lancet 2000;356:1099



QuantiFERON®-TB Gold Plus

Mitogen – Positive Control

Low response may indicate inability to generate IFN- γ

Nil – Negative Control

Adjusts for background IFN- γ

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses

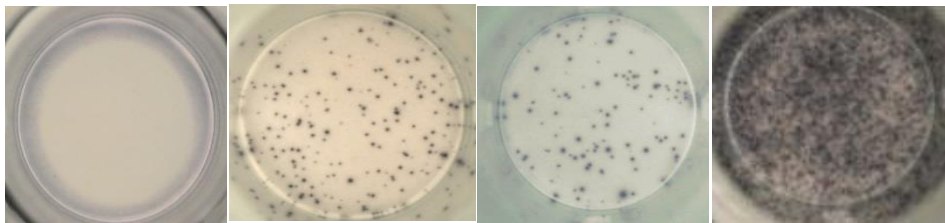


- Essentially 2 tests in one blood draw
- TB1 and TB2 should be close in value



T-Spot.TB (T-Spot)

- Collect blood in CPT tube
- Recover, wash, & count PBMCs
- Aliquot 250,000 PBMCs to 4 wells with anti-IFN- γ
- Add saline, PHA, ESAT-6 or CFP-10 & incubate
- Wash away cells
- Develop & count spots where cells produced IFN- γ

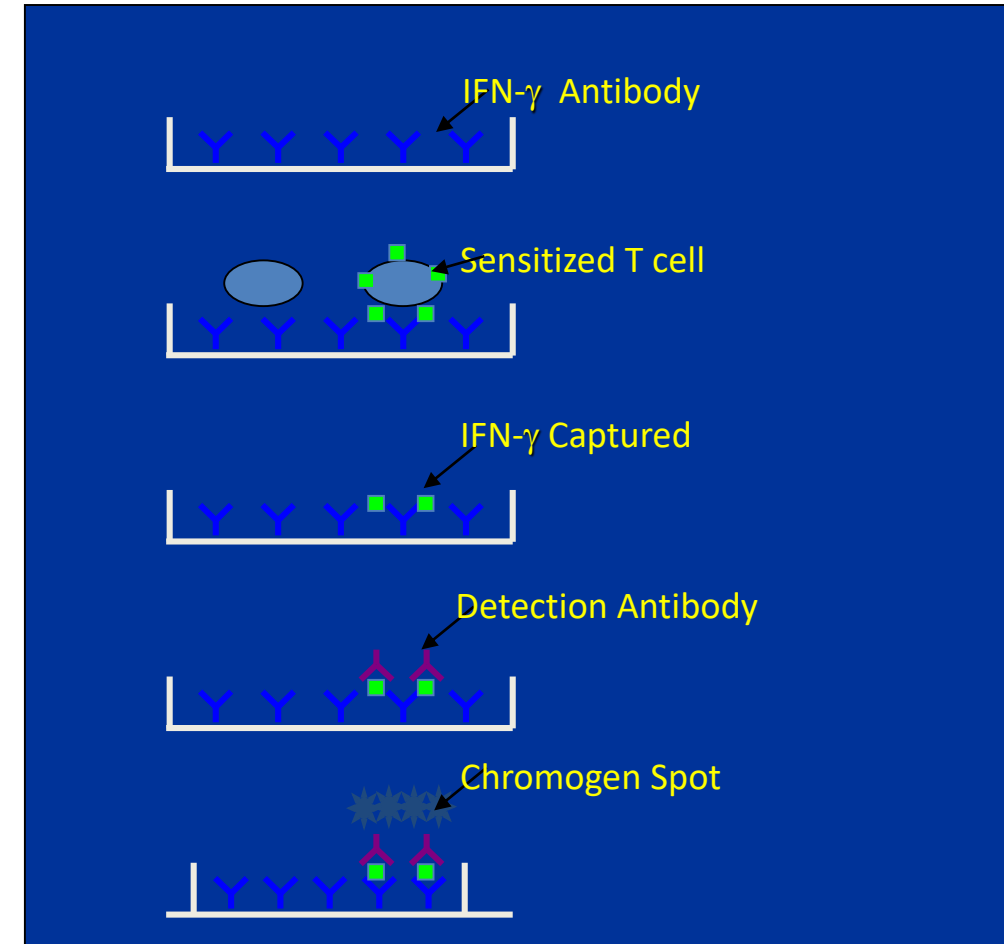


Saline

ESAT-6

CFP-10

PHA



Indeterminate and Borderline Results

- Indeterminate
 - Negative control result is too high
 - High background production of IFN- γ
 - Positive control result is too low
 - Immunocompromised patients may not respond to mitogen
 - Indeterminate Results Should be Repeated – you don't have an answer!
 - Either repeat the original test or choose another option
- Borderline (T-Spot only)
 - Falls within borderline zone close to negative/positive cut point
 - May consider as a positive for immune suppressed or those who are recent contacts to TB



Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

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ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- **Recommend** IGRA rather than TST for persons ≥ 5
 - 1) likely to be infected with MTB
 - 2) **low or intermediate risk** of progression to disease
 - 3) decided testing is warranted and
 - 4) *have either a history of BCG or are unlikely to return for reading*
 - **(Strong recommendation, moderate quality evidence)**
 - TST acceptable if IGRA not available, too costly, too burdensome.

CID 2016



ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- **Suggest** IGRA rather than TST for all other persons ≥ 5 :
 - 1) likely to be infected with MTB
 - 2) **low or intermediate risk** of progression to disease
 - 3) decided testing is warranted and
 - *(Conditional recommendation, moderate quality evidence)*
 - TST acceptable if IGRA not available, too costly, too burdensome.

CID 2016



ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- **Insufficient data to recommend a preference either a TST or IGRA** for all other persons ≥ 5 :
 - 1) likely to be infected with MTB
 - 2) have a *high risk* of progression to disease
 - 3) decided testing is warranted

CID 2016



ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

Guidelines **recommend** persons at low risk for MTB infection and disease progression NOT be tested.

- If testing is performed in those unlikely to be infected despite guidelines to contrary:
 - We **suggest performing an IGRA instead of a TST.**
 - (*conditional recommendation, very low-quality evidence*)
 - We **suggest a 2nd diagnostic test if initial test positive**
 - Confirmatory test may be either IGRA or TST
 - Person **considered infected only if both tests positive.**
 - (*conditional recommendation, very low-quality evidence*)

CID 2016



ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- We **suggest performing a TST rather than an IGRA** in healthy children under 5:
 - 1) for whom it has been decided testing is warranted
 - *(conditional recommendation, very low-quality evidence)*

2018 Pediatric Red Book recommends
IGRA down to age 2

CID 2016



Treating TB Infection

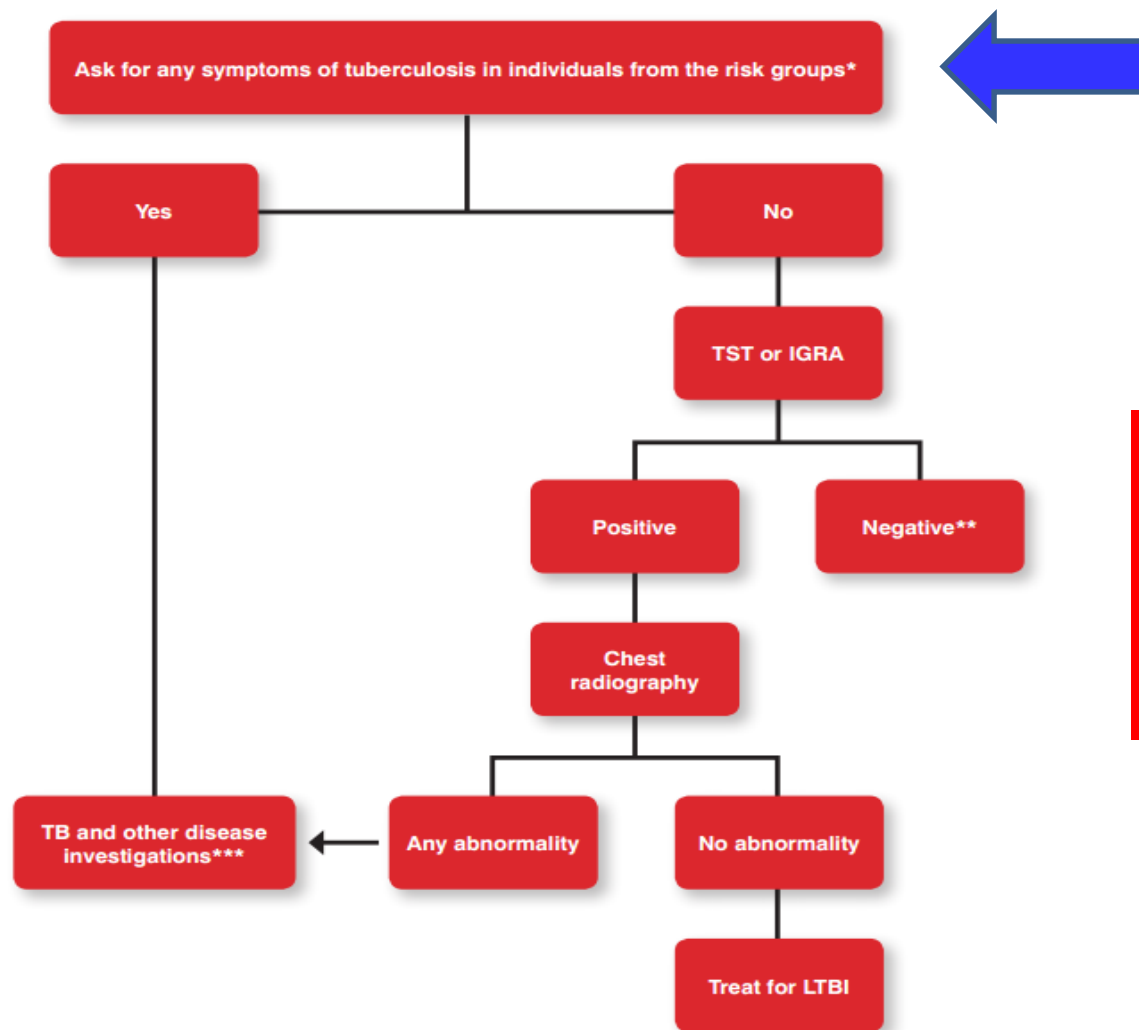
Wait –
Are We
There Yet?



“NO!”



Figure 1. Algorithm for targeted diagnosis and treatment of LTBI in individuals from risk groups



WHO Guidelines
on the
management of
latent
tuberculosis
infection 2015

Remember
that the TST
or IGRA may
be negative
in those
with active
TB!

* Any symptoms of TB include any one of: cough, haemoptysis, fever, night sweats, weight loss, chest pain.



Active TB Disease or TB Infection?

The Clinical Evaluation

The single most important thing prior to starting treatment for TB Infection is to exclude active TB disease.

If in doubt – wait!

Evaluate for TB disease

Consider consultation with TB expert



Evaluate to Exclude Active TB Disease

- If the TST or IGRA is Positive –
 »OR
- Child < 5 or immunocompromised person with recent exposure **even if TST/IGRA negative** -
 - ✓ History
 - ✓ Physical examination
 - ✓ Chest X-Ray



Evaluation for TB when IGRA Positive, Patient has Symptoms or is Immunocompromised.

- Testing for TB infection ✓
- Medical history
- Physical examination
- Chest radiograph
- Bacteriologic or histologic exam



Is There Evidence of Disease?

- Symptoms*
 - Fever
 - Chills
 - Night Sweats
 - Weight Loss
 - Cough (dry/productive)
 - Hemoptysis
 - Fatigue

* **only one may be present**

Is Patient at Risk of Progression to Disease?

- Medical History:
 - HIV
 - Silicosis
 - Chronic Kidney Disease
 - Diabetes
 - Immunosuppression
 - Drug/alcohol/tobacco
 - TB exposure



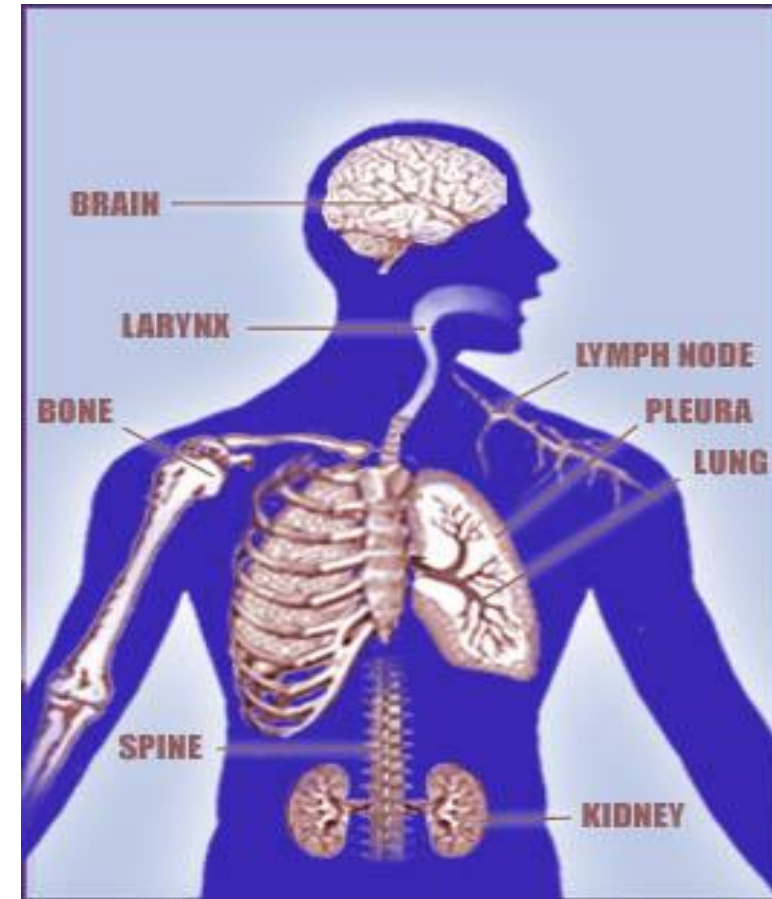
Physical Exam

- General assessment – does person look well?
- Lung exam
- Check for lymph nodes
- Palpate liver
- *In children* look at growth curve/weight/activity
- Look for anything that will complicate therapy!



TB Exam – Focus on Possible Sites of TB Disease

- Lungs – Pulmonary
- Extrapulmonary
 - Larynx
 - Lymph nodes (cervical inguinal, supraclavicular, mediastinal, abdominal)
 - Pleural effusion
 - Genitourinary
 - Bones & joints
 - Miliary (disseminated)



Radiologic Exam

- CXR must be done **before treatment of TB Infection**
 - Must be read as normal
- Or
- IF abnormal:
 - Not consistent with Active TB
 - Stable abnormality confirmed over a 3 month period



CXR - Can Suggest TB Disease but Does Not Definitely Diagnose or Exclude TB Disease

Cavitary lesions

Upper lobe infiltrates

Pleural effusion especially in those with recent exposure

“Tree in bud” findings on CT exam

Common mimics of TB =

- Non-tuberculous mycobacteria (NTM)
- fungal infection
- bacterial abscesses
- necrotic neoplasm (especially lung neoplasm)



Usually thin walled cavities

May be Normal!



CXR – Old Healed TB

- Nodules & fibrotic lesions may contain slowly multiplying bacilli; these persons have a higher risk for progression to active TB disease
 - CXR consistent with old TB and a positive TST/IGRA should have high priority for LTBI treatment

Caution: I usually have several patients in the San Antonio TB Clinic with positive cultures for TB and a CXR report that says c/w old healed TB.

If the CXR is “stable” for 2 – 3 months this is an indication that abnormality represents latent TB infection

If the CXR shows calcified nodular lesions (calcified granuloma) there is a very low risk for progression to TB disease



Laboratory Examination

- AFB smear
- AFB culture
- Nucleic acid amplification test (NAAT)
 - GeneXpert (pcr)
 - Molecular Detection of Drug Resistance (MDDR)



Bacteriologic and Histologic Examinations

When lung or larynx is site of disease and for every patient with extrapulmonary TB:

- 3 sputum specimens for AFB smear and culture; request a pcr on initial specimen if risk of TB disease
- Collected 8-24 hours apart with at least 1 early morning specimen
 - one induced specimen
 - one observed specimen



Bacteriologic and Histologic Examinations

Extrapulmonary Specimens

- Urine
- Cerebrospinal fluid *
- Pleural fluid *
- Pus
- Biopsy specimens

*recovery poor



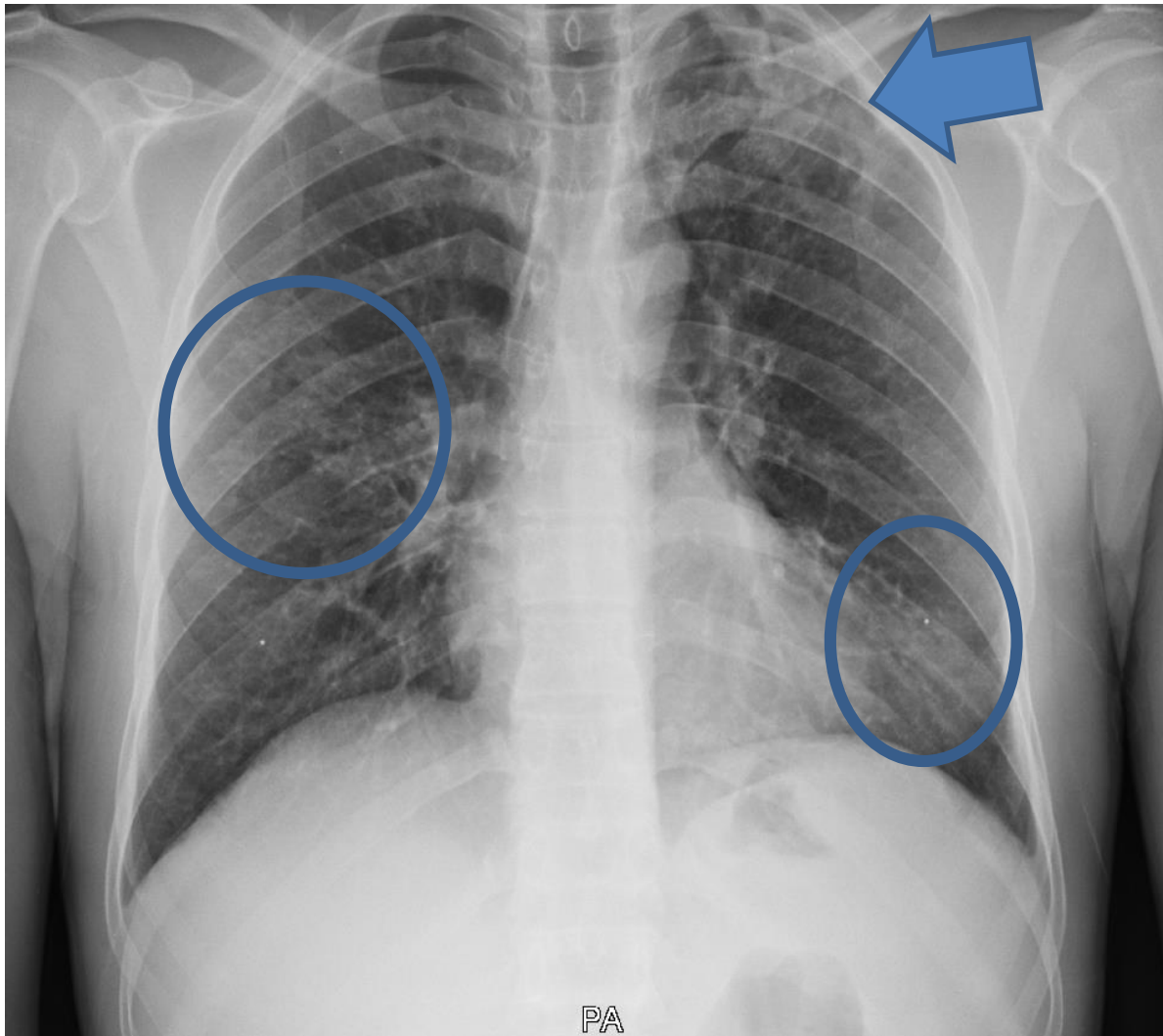
**Do NOT collect
specimens in Formalin**



Case Study -Immigrant Evaluation For TB 2017

- 13 year old immigrated from Northeastern African country within last year
 - Thin but otherwise well
 - Positive T-Spot
 - Normal CXR
- What is the Diagnosis?**





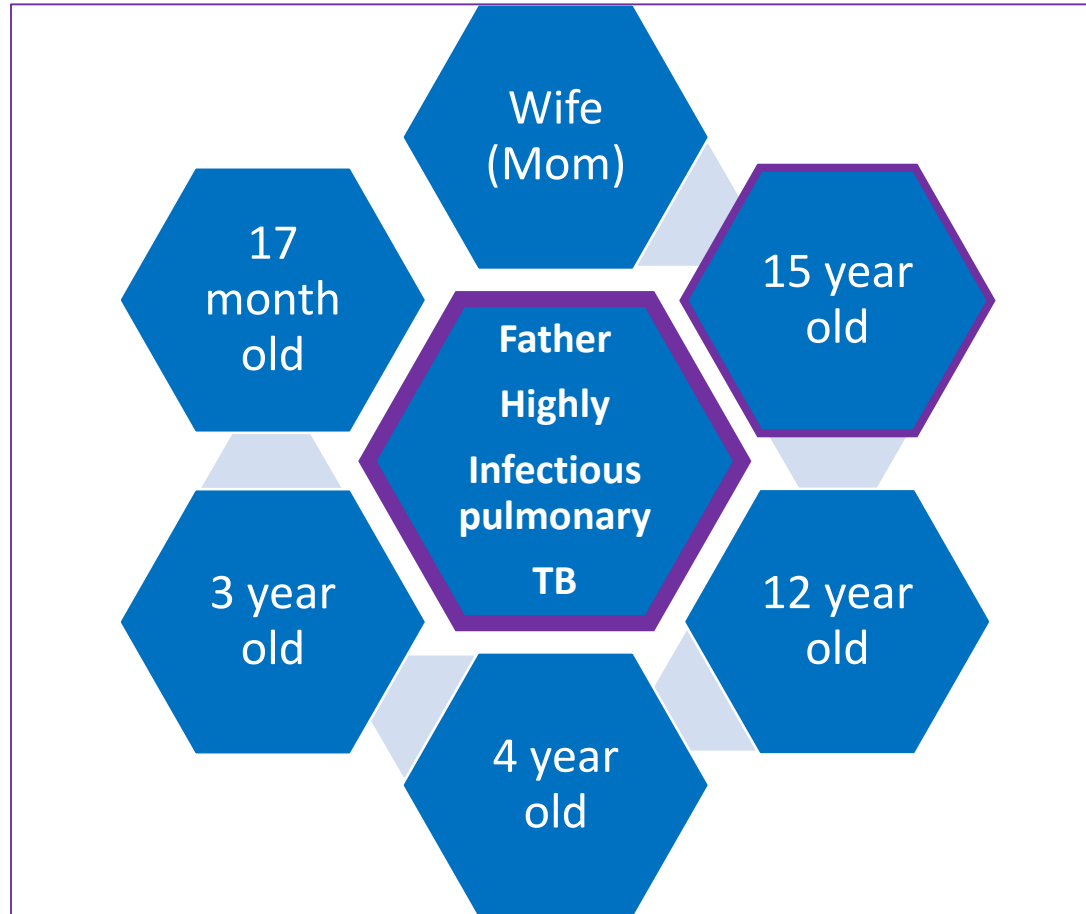
May 2019

**37 year old African man
4 months of cough, weight
loss, and poor energy
6 weeks after starting TB
treatment remains strongly
AFB smear positive**

AFB – Acid Fast Bacilli

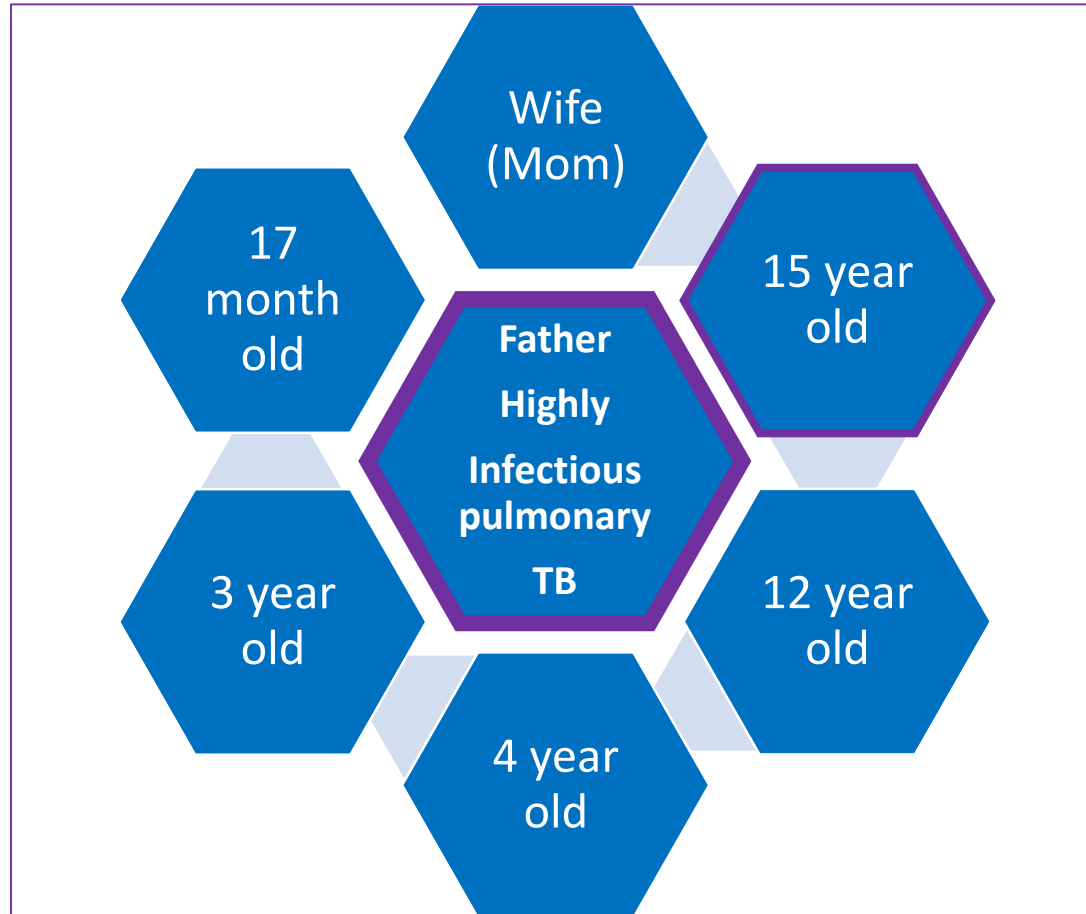


Family of Newly Diagnosed Patient Comes to Clinic – What Now?



- 1
- 2
- 3
- 4
- 5

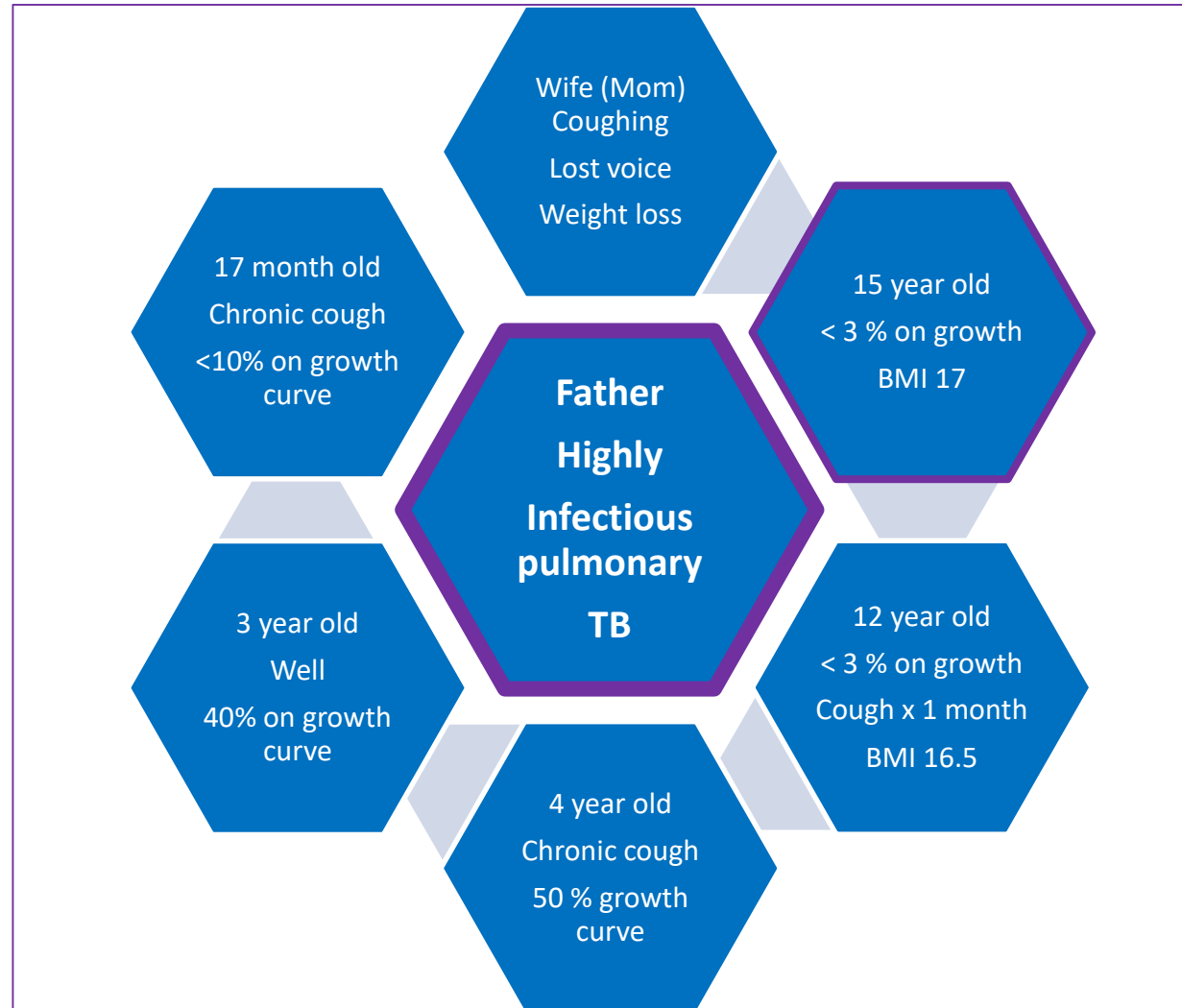
Family of Newly Diagnosed Patient Comes to Clinic – What Now?



- IGRA – except 17 month old
 - BCG vaccinated
 - TST for children < 2
- Evaluate for symptoms of TB; generally do they look well? Kids playful?
- Medical Assessment
 - Weight, BMI, Growth scale for kids
 - Targeted exam – lungs, lymph nodes
- CXR
- Sputum if coughing

2019 Contact Investigation in Family

Epidemiology is Critical Information



2019 Contact Investigation in Family

All IGRA positive except 17 month old - 20 mm blistering TST



Why Should Small Children Who Are Exposed to Active TB Disease Be Treated Even When TST or IGRA is Negative?

**What if
the 17
month old
was TST
negative?**

- Very high rate of infection
- Takes up to 3 months for the skin test to turn positive
 - Small children can very quickly become very sick
- U.S. studies – 10% to 20% of childhood TB cases can be prevented if children exposed in a household are treated
- WHO standards – children <5 years old exposed in a TB household should be treated



Percent Risk of Disease if Infected by Age

Age at Infection	Risk of Active TB
Birth – 1 year*	43%
1 – 5 years*	24%
6 – 10 years*	2%
11 – 15 years*	16%
Healthy Adults	5-10% lifetime risk
HIV Infected Adults ⁺	30-50% lifetime

*Miller, Tuberculosis in Children Little Brown, Boston, 1963

⁺WHO, 2004



Risk of Progression to TB Disease by Age

<u>Age @ primary infection</u>	<u>Risk of Disease</u>	
	Disease	up to 50%
• Birth - 12months	Pulmonary Disease	30-40%
	Miliary or TB Meningitis	10-20%
	Disease	20-25%
• 1-2 years	Pulmonary Disease	75%
	Miliary or TB Meningitis	2-5%



Treatment of LTBI

Special considerations



Deciding When to Treat LTBI

Groups Who Should be Given High Priority for LTBI Treatment

People with a positive IGRA result or a TST reaction of ≥ 5 mm

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on CXR c/w old TB
- Organ transplant recipients
- Persons immunosuppressed for other reasons
 - taking the equivalent of >15 mg/day of prednisone for ≥ 1 month,
 - taking TNF- α antagonists
 - receiving chemo/radiation therapy

People with a positive IGRA result or a TST reaction of ≥ 10 mm

- Persons from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology lab personnel
- Children < 4 years of age,
- Children and adolescents exposed to adults in high-risk categories



Why Should Small Children Who Are Exposed to Active TB Disease Be Treated Even When TST or IGRA is Negative?

- Very high rate of infection
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AIDSinfo: Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

- **Treating LTBI (to prevent TB disease) - Indications:**
- (+) screening test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB **(AI)**
- Close contact with a person with infectious TB, regardless of screening test result **(All)**

<https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0>

Last updated: Sept 22, 2017; last reviewed: September 22, 2017)



HIV Positive Persons

- All HIV positive persons with TB infection should be treated
- Careful evaluation is needed to exclude TB disease – CXR, symptom screen, sputum if any symptoms present
 - Remember in HIV + persons a positive TST is 5mm or >
 - Both IGRA and TST may be negative – if recently exposed should be treated despite negative screening tests. These may be negative > 10 % of the time.



Management of Positive TST or IGRA

When CXR is Abnormal c/w TB disease or If Patient Has Signs or Symptoms of Active TB Disease

- The patient should be suspected of having TB disease
- Collect 3 sputa for smear and culture
- Strongly consider starting standard 4 drug (RIPE) treatment – if started report!
- If positive smear and/or Gene Xpert
 - Report to public health and start 4 drug (RIPE) treatment
- Never (ever!) start a treatment for TB infection in a patient with possible active TB



Treatment Options for LTBI

- INH +RPT once weekly
- Rifampin daily
- INH 9 daily
- INH 6 daily
- 12 weeks (12 doses)
- 4 months (120 doses)
- 9 months (270 doses)
- 6 months (180 doses)

The longer the duration/more doses, the less likely your patient is to complete treatment

Fewer than 60% complete 9 months of INH



Rifampin Treatment of TB Infection

- Pros:
 - Higher Completion Rates
 - Equally effective
 - Fewer Side Effects
 - Less Hepatotoxicity
 - Cost effective
 - Rifampin resistance uncommon
 - Globally 3%
- Cons:
 - Drug Interactions
 - Hormone Contraceptives
 - Warfarin
 - Prednisone
 - **HIV Antiretroviral agents**
 - And many more...must look up all drugs for interactions
 - Orange Body Fluids
 - Other Potential Side Effects (rare):
 - Rash
 - Thrombocytopenia
 - Anemia
 - Leukopenia
 - Allergic Interstitial Nephritis



Think TB

TREATMENT IS PREVENTION – WE DO NOT HAVE AN
EFFECTIVE VACCINE – YET

TREATMENT STOPS TRANSMISSION

